UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/867,034	05/29/2001	Roberto A. Macina	DEX-0207	5629

26259 7590 05/21/2002

LICATLA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER
DAVIS, NATALIE A

ART UNIT	PAPER NUMBER
1642	8

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 09/867,034	Applicant(s) MACINA ET AL.	
	Examiner Natalie A. Davis	Art Unit 1642	

-- The MAILING DATE of this communication appears on the c v r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *2-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group I, claims 1(a) and (c) and 14, species SEQ ID NO: 5 in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the inventions are not independent or distinct, as a proper search of Group I should reveal art relating to Groups II-VIII and searching 22 sequences would not be an undue burden. This is not found persuasive because an independent search of each sequence, a fragment thereof and variations thereof does pose an undue burden and Groups II-VIII are distinct inventions as indicated in the previous office action.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1(a) and (c) and 14, species SEQ ID NO: 5 (as it reads on polynucleotides) are being examined as belonging to the elected Group I, while claims 2-13 are withdrawn from examination as being drawn to a non-elected invention.

Information Disclosure Statement

The information disclosure statement filed 20 September 2001 has been considered. A signed copy is attached hereto.

Specification

1. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 14 is drawn to a vaccine for treating colon cancer, however, the disclosure makes no mention of using a vaccine in the treatment of colon cancer. moot

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

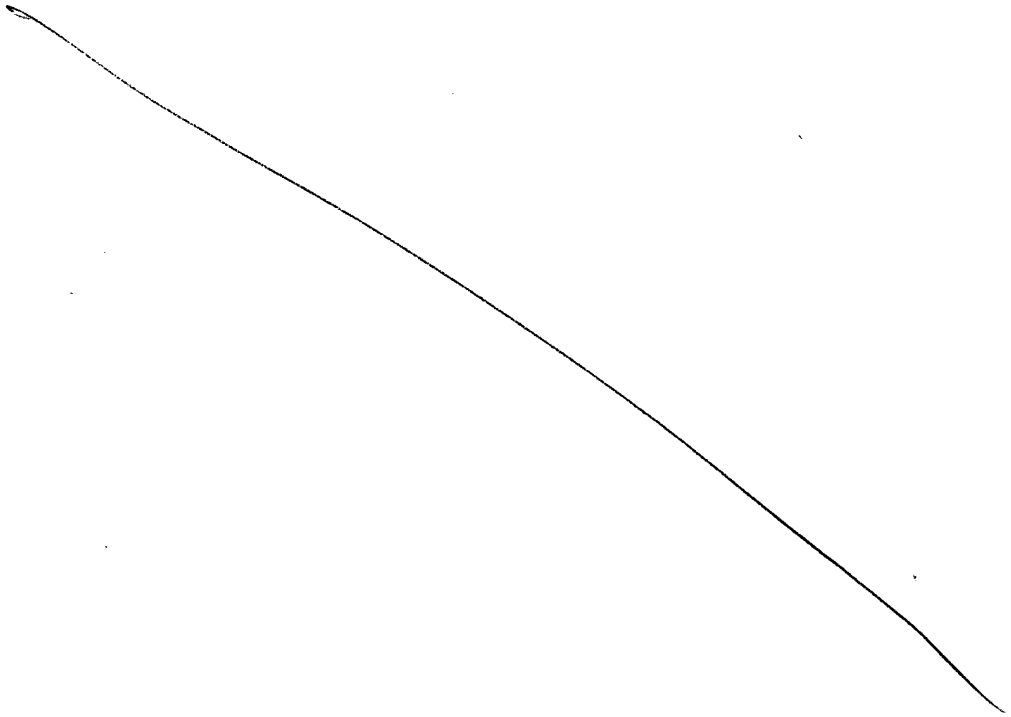
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1(a) and (c) and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide comprising SEQ ID NO: 5, does not reasonably provide enablement for a variant of a polynucleotide comprising SEQ ID NO: 5 or a polynucleotide capable of hybridizing to the antisense sequence of SEQ ID NO: 5.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification discloses the polynucleotides of the invention as colon specific genes or CSG's (p. 1), which are believed to be useful in assays for detecting, staging, monitoring, progonosticating, imaging and treating cancers (p. 3). Polynucleotides are disclosed as any RNA or DNA, as well as modified RNA and DNA. They may comprise nucleic acid sequences comprising single- and double-stranded DNA, that is a mixture of single- and double-stranded regions, single- and double-stranded RNA or triple stranded regions of DNA, RNA or both.. Likewise, the polynucleotide may comprise modified bases such as inosine or tritylated bases (p. 9).

The nature of the invention is to a variant of a polynucleotide comprising SEQ ID NO: 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. There are many polynucleotides that may or may not perform the same biological functions and the specification does not give any guidance to which molecules having single- and/or double-stranded, triple stranded regions of DNA, RNA or both, or which comprise modified bases of SEQ ID NO: 5 will exhibit the biological activities as the claimed, or any guidance as to which regions of the sequence must be preserved so the molecule will function as claimed. Thus, it would be an undue burden to one of ordinary skill in the art to assay for claimed sequences, which are capable of functioning as contemplated. One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any polynucleotide variant of SEQ ID NO: 5 and applicant has not enabled all of these types of modifications because it has not been shown that these polynucleotides are capable of functioning as that which is being disclosed. Likewise, proteins encoded by variant polynucleotides may or may not function as contemplated.



Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Rèsidues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the breadth of the claims and enablement set forth, and it cannot be predicted from the disclosure how to use any and all variants of SEQ ID NO: 5 and variant protein derived therefrom. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

moot

4. Claims 1 (c) and 14 are drawn to polynucleotides, which hybridizes to antisenese sequence of SEQ ID NO: 5. Lehninger, et al. (Principles of Biochemistry, 2nd Ed., Worth Publishers, NY, 1993) is cited in order to establish the general state of the art and the level of predictability of hybridization. Lehninger, et al. teach that hybridization requires the pairing of nucleotide bases of two nucleic acid strands which are complementary (p. 343) and teaches that complementary strands are not identical in either base pair sequence or composition, that is wherever adenine appears in one chain, thymidine is found in the other and wherever guanine appears in one chain, cytosine is found in the other (p. 335). Applicant has not taught how to hybridize identical nucleic acid strands or a polynucleotide to a single- and/or double-stranded, triple stranded regions of DNA, RNA or both, or which comprise modified bases of SEQ ID NO: 5. In addition, the specification does not disclose whether the polynucleotides sequences hybridize partially or completely or which regions of the strands are hybridizing. The specification defines polynucleotides as nucleic acid sequences comprising single- and double-stranded DNA, that is a mixture of single- and double-stranded regions, single- and double-stranded RNA or hybrids thereof, but does not provide any guidance as to how one would hybridize the various polynucleotides. In view of the Lehninger, et al. teaching, one of ordinary skill in the art would not clearly expect to be able to hybridize a polynucleotide to the antisense of SEQ ID NO: 5. One cannot extrapolate the teachings of the specification to the breadth of the claims because the claims are broadly drawn to any polynucleotide which hybridizes to the antisense of SEQ ID NO: 5 and applicant has not enabled all of these types of hybridizations because it has not been shown that these polynucleotides are capable of hybridizing. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

5. The nature of the invention is to treatment of colon cancer using CSG. Orkin et al. is cited in order to establish the general state of the art and the level of predictability of the prior art of gene therapy. Orkin et al (Report and Recommendations of the Panel to Assess the NIH investment in Research on Gene Therapy, 1995) state that "while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the

initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols" and further teach that significant problems remain in all basic aspects of gene therapy. In addition, Marshall (Science, 1995, 269:1050-1055) teaches that there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (p. 1050, col 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (p. 1054, col 3). Anderson (Nature, vol. 392, suppl. 1998, pp. 25-30) and Inder, et al., (Nature, vol. 389, 1997, pp. 239-242) also teach gene therapy has no notable clinical successes and it will take years of research before the new technology will make a noticeable impact on the treatment of disease and becomes a part of routine practice in medicine. Furthermore, the research community, as reported by Nature Biotechnology, 1997, 15:815, has responded to the issues raised in the Orkin Report drawn to vector based delivery systems, that is the critical steps of delivery of a gene to the right cell and the subsequent maintenance of gene expression, since it is now widely appreciated that the natural tropism of a virus, while advantageous to its own replication cycle is not always optimal for a gene delivery protocol and a number of laboratories have explored methods to redirect the targeting that has evolved to ensure viral infectivity in ways that may be more suitable to the aims of gene therapy and concludes that this return to first principles should help to continue to move gene therapy in the direction of its largest and most important ambitions (p. 815). Clearly, the issues raised by the Orkin report, although being addressed, have not been resolved. In view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed

6. The nature of the invention is to a vaccine for the treatment of colon cancer. The specification provides no exemplification of or guidance on how to use the claimed vaccine in the treatment of colon cancer. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to

eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1). In view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

7. Claims 1(a) and (c) and 14 are rejected under 35 U.S.C. 112, first paragraph. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Vas-Cath Inc. v. Mahurkar (CA FC) 19 USPQ2d 1111 (6/7/1991) clearly states that "written description" of invention required by first paragraph of 35 U.S.C. 112 is separate and distinct from that paragraph's requirement of enabling disclosure, since description must do more than merely provide explanation of how to "make and use" invention; applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed. An applicant shows possession by describing the claimed invention with all it limitations using such descriptive means as words, structures, diagrams, and formulas. Also, description of an actual reduction to practice, or by showing the invention was "ready for patenting," or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention at the time of filing.

The claims are drawn to a polynucleotide variant of SEQ ID NO: 5 and a polynucleotide capable of hybridizing to antisense of SEQ ID NO: 5?

The specification discloses that polynucleotides of the present invention may comprise single-, double-, and triple- strands of DNA and /or RNA, but does not disclose the isolation of and assaying of molecules, or any variants of SEQ ID NO: 5. There is no actual reduction to

practice, sufficient descriptive information, such as definitive structural features, which are critical to polypeptide activity, or complete detailed description of the function of claimed invention indicating that the claimed nucleic acids were indeed isolated, produced, and assayed for the uses disclosed. Likewise, there are no examples disclosed that conveys to one of skill in the art that the applicant was in possession of any vaccine for the treatment of colon cancer, as there is no descriptive information, such as how to make and administer the vaccine or complete detailed description of the function of claimed invention indicating that the vaccine was indeed identified and used for the treatment of colon cancer. Thus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the invention asclaimed.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1(c) is rejected under 35 U.S.C. 102(b) as being anticipate by Peinado, et al., (1992).

Peinado, et al. (Proc. Natl. Acad. Sci., USA, 1992, 89:10065-69), teach arbitrarily primed polymerase chain reaction (AP-PCR) to detect somatic genetic alterations in tumors of the colon and rectum using arbitrary primers, which hybridize under stringent conditions to numerous sequences in the total geneomic DNA (p. 10065). It is inherent that the polynucleotide primer may hybridize to a portion of anitsense sequence of SEQ ID NO: 5 under stringent conditions. This rejection may be overcome if the claim were to recite a polynucleotide, which completely hybridizes to the full length of antisense sequence of SEQ ID NO: 5 or some language supported by the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Natalie A. Davis whose telephone number is 703-308-6410. The examiner can normally be reached on M-F 8-5:30 (every other Friday off).
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa PhD can be reached on 703-308-3995. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-308-4315 for regular communications and 703-308-4556 for After Final communications.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Natalie A. Davis, Ph.D.
May 15, 2002

Sheela 9. Huff
SHEELA HUFF
PRIMARY EXAMINER